American Journal of Medical Genetics 62:365–371 (1996)

Autosomal Recessive Disorder With Muscle Contractions Resembling Neonatal Tetanus, Characteristic Face, Camptodactyly, Hyperthermia, and Sudden Death: A New Syndrome?

Giangiorgio Crisponi

Centro per lo Studio delle Malformazioni Congenite, Istituto di Puericultura e Patologia Neonatale, Università di Cagliari, Italy

This work describes an autosomal recessive syndrome observed over the past 25 years in 17 newborn babies (8 males, 9 females), from 12 different families in Southern Sardinia. This disorder is evident at birth and is characterized by marked muscular contraction of the facial muscles in response to tactile stimuli or during crying, with trismus and abundant salivation simulating a tetanic spasm. The contractions slowly disappear as the infant calms. There is also neck muscle hypertonia with a tendency to opisthotonus. All patients present facial anomalies such as large face, chubby cheeks, broad nose with anteverted nostrils, and long philtrum. The hands show bilateral camptodactyly. The clinical course in all patients was characterized by marked feeding difficulties and appearance of variable fever at about 38°C, with peaks of irregular hyperthermia of over 42°C, with onset ranging from birth to a few weeks. In some patients these symptoms were accompanied by generalized seizures. Death occurred after a period of a few weeks to some months and coincided with fever above 42°C. Laboratory investigations performed in all of these cases did not give any useful pathogenetic indications. Only patients 10 and 16 are still alive today. Patient 10 is now 14 years old. She presents slow regression of the dystonic symptomatology, while dysthermia and mild psychomotor delay persist. © 1996 Wiley-Liss, Inc.

KEY WORDS: muscle contractions, camptodactyly, hyperekplexia, startle disease, hereditary stiff-baby syndrome, Isaacs-Mertens syndrome, GABA receptor

INTRODUCTION

In this work we describe an apparently new autosomal recessive syndrome usually with fatal outcome, characterized by muscular contractions with onset at birth, intermittent hyperthermia, facial anomalies, and camptodactyly. Though the clinical aspects are very similar to other conditions such as neonatal tetanus, hereditary hyperekplexia, or Isaacs-Mertens and stiff-baby syndromes, remarkable clinical and laboratory differences are present indicating that this is a distinctive condition with a more severe clinical course. Because a very low level of cerebrospinal fluid (CSF) gamma-amino butyric acid (GABA) was found in the last patient observed, we speculate that the anomaly might be due to a congenital defect resulting in low concentration of GABA.

We describe here the clinical, genetic, and neurological aspects in 17 patients from 12 unrelated Sardinian families.

CLINICAL REPORTS

The 17 patients (8 males, 9 females; Table I) came from 12 unrelated families from Southern Sardinia. There was no parental consanguinity and the parental age did not appear to be increased. In the pedigrees, we observed healthy sons in some families. Other than patients described, no other member of the family presented any aspects of the syndrome.

The phenotype and clinical evolution of this syndrome overlap in all 17 cases. The phenotypic manifestations of the syndrome were already evident at birth. Typical findings included round face, full cheeks, prominent cheekbones, broad nose with anteverted nostrils, and long philtrum. Micrognathia, torticollis,

Received for publication August 1, 1994; revision received November 1, 1995.

Address reprint requests to Giangiorgio Crisponi, Centro per lo Studio delle Malformazioni Congenite, Istituto di Puericultura e Patologia Neonatale, Via Ospedale 119, 09124, Cagliari, Italy.

TABLE I. Clinical Manifestations in 17 Patients From 12 Families

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Family	A	A	B	C	C	D	E	E	E	E	F	M	H	I	J	K	L
Sex	F	M	M	F	M	F	M	M	F	F	F	M	M	F	F	F	M
Gestation (weeks)	39	38	40	37	37	40	40	33	37	35	NA[a]	38	41	42	41	28	40
Age (days) at admission	15	3	5	1	1	2	13	1	4	1	20	1	2	3	1	1	1
Age (weeks) at death	7	3	9	2	4	1	5	12	8	Alive	10	7	2	28	72	Alive	12
Muscle contraction	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large face	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Broad nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Anteverted nostrils	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Long philtrum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Full cheeks	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Micrognathia			+			+					+						+
Torticollis	+										+						+
Camptodactyly	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seizures					+		+	+						+	+		+
Hyperthermia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Feeding difficulties	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Birthweight (g)	3,400	4,000	3,700	3,300	3,670	2,500	3,100	2,170	2,550	2,730	3,250	2,650	3,680	3,000	3,050	980	3,490
EMG abnormalities	NE[b]	NE	—[c]	NE	NE	NE	NE	NE	NE	—	—	—	—	NE	NE	—	—
EEG abnormalities	NE	NE	NE	NE	NE	NE	NE	NE	NE	—	—	—	—	NE	—	+	—
Chromosomes	NE	—	NE	NE	—	NE	NE	—	—	—	—	—	NE	NE	NE	NE	—

[a] Not available.
[b] Not examined.
[c] Normal result.

and scoliosis were occasionally present. The hands showed bilateral camptodactyly, with the index finger positioned over the 3rd, and the 5th over the 4th. Sometimes the feet presented anomalies such as overlapping toes, rocker-bottom feet, and prominent talus. In one patient, hypospadias was present. The birth weight, length, and head circumference were appropriate for the gestational age. Routine hematological and biochemical investigations were always in the normal range. Serum levels of creatinine, blood urea nitrogen, ammonia, glucose, uric acid, transaminase, gamma glutaryl transferase, alkaline phosphatase, creatine kinase, bilirubin, total protein, albumin, cholesterol, triglyceride, and immunoglobulins were normal. Serum concentrations of sodium, potassium, calcium, magnesium, chloride, and phosphorus levels were normal. Urine and blood amino acid chromatography, organic acids, and screenings for lysosomal defects were normal. When performed, brain ultrasound, computed tomography (CT) scan, and magnetic resonance imaging (MRI) of the brain showed no abnormalities. The muscle-specific enzymes and carnitine were within the normal range. Muscle biopsies analyzed with different histological staining methods and immunohistochemical reactions were normal. Electromyography (EMG) performed on contracted muscles showed a full electromyographic interference pattern, without myotonic discharges. Because of severe, protracted fever, infectious agents were repeatedly sought, but cultures for bacterial, fungal, and viral infections, as well as inflammation indices were consistently negative. Biological tests for tetanus were negative. Chromosome analysis did not show any anomalies.

In all cases, when examination was attempted, or during nursing procedures for bathing, feeding, and changing diapers, a state of massive muscular contraction occurred. This especially involved contraction of the mimic muscles of the face into an expression resembling that of a tetanic spasm with an appearance of risus sardonicus. The patients presented contractions of the orbicular muscles of the eye with lacrimation, and contractions of the masseter and orbicular muscles of the mouth with copious emission of foaming saliva, probably due to contraction of the oropharyngeal muscles with the inability to suck or swallow. Crying appeared as a continuous weak lament, emitted in forced expiration, followed by short apneic spells with cyanosis. The muscles of the neck were contracted with hyperextension of the head and opisthotonus. The upper limbs were usually flexed and the arms adducted to the trunk. The forearms were flexed and showed resistance to passive extension; and the hands were clenched. In contrast, there was no particular contraction of the abdominal wall. The lower limbs presented a minor tendency to stiffening. Irregular movements were present, with occasional jerking at the large joints. Involuntary jerks were exacerbated by external stimuli. Sometimes the trunk became stiff and presented torsion and bending. Even the respiratory muscles were involved in the contraction phenomena, with dyspnea, a tendency to cyanosis, and short apneic spells during prolonged crying. Such episodes of spasmodic contraction were of

variable duration. When the baby was quiet or stopped crying, the contraction usually stopped after a few minutes. During rest, the patient recovered a normal relaxed appearance. During sleep, contraction phenomena never were manifested. During sleep and rest, the muscle tone always seemed normal. Deep tendon reflexes were elicited easily. Contraction phenomena tended to become less frequent during the weeks and months following birth. They were observed after painful stimuli or during crying and were particularly exacerbated during fever episodes.

Fever, the other typical manifestation of the syndrome, appeared a few days to a few weeks after birth. It had an intermittent character not linked to any infectious diseases and presented occasionally with peaks over 42°C with rapid falls. Hyperthermia was usually preceded by a state of restlessness, continuous crying, spasms of the facial muscles, abundant salivation, and vasomotor phenomena with reddening of the face. On such occasions, tachypnea, a tendency to cyanosis, and tachycardia were noted. During these episodes, occasional generalized seizures of variable length were observed. Soon afterward, the patient entered a state of shock, with generalized muscular hypotonia and absence of response to stimuli. The skin appeared diffusely pale and marbled and this was followed by bradypnea with a tendency to apnea. Death usually occurred following one of these episodes. Pharmacological attempts to control either contractions or hyperpyrexia with drugs such as diazepam, phenobarbital, phenytoin, vigabatrin, or dantrolene were always unsuccessful.

The pedigrees of the 12 families are presented in Figure 1. Considering the close similarity in the clinical characteristics and in the evolution of the condition, only one patient is described in detail. The remaining cases are presented only by photographs (Figs. 2, 3) and in Table I.

Family L (Patient No. 17)

M.L., a full-term male infant, was the first child of healthy, nonconsanguineous parents. The mother was 26 years old, and the father 28. Birth weight was 3,490 g (50th centile), length 52 cm (50th centile), and OFC 35 cm (50th centile). The patient came from a small village in Central Eastern Sardinia with a high rate of inbreeding. A great-grandparent of the child is apparently a cousin to a great-grandparent of patient No. 6, who came from the same village. Soon after birth, the patient was transferred to our nursery because of unusual appearance and muscle contraction resembling neonatal tetanus. Physical examination demonstrated a round, large face, puffy cheeks, prominent cheekbones, broad nose with anteverted nostrils, long philtrum, left choanal stenosis, micrognathia, torticollis on the right, mild scoliosis and bilateral camptodactyly, with the index finger overlapping the 3rd and the 5th finger over the 4th (Fig. 3). The following foot anomalies were also observed: clubfoot, 2nd toe overlapping the first bilaterally, and 5th toe over the 4th on the left. The upper limbs were held in forced flexion adducted to the trunk. During nursing care, contraction involving mainly the facial and neck muscles appeared, and flexion of the limbs was accentuated, with clenched hands. The facial contraction became more evident during crying, and involved particularly the masseter and the orbicularis muscles of the eye and mouth, as in a tetanic crisis. The contraction also involved the neck muscles, with hyperextension and deviation of the head to the right, followed by bending of the trunk with twisting movements. It is probable that contractional phenomena also involved the oropharyngeal muscles, preventing swallowing and causing the emission of large quantities of foaming saliva. The cry was weak. As crying persisted, cyanosis and a tendency to spells of apnea were manifest, probably related to spasm of the respiratory muscles. These phenomena were easily elicited and ceased immediately when the child stopped crying, at which time he recovered a serene expression with normal muscle tone. During sleep or rest, stiffness was never manifest. Clinical follow-up lasted until death at 3 months. The clinical course was characterized by the persistence of contraction phenomena elicited by disturbing stimuli, by the inability to feed spontaneously with absence of sucking and swallowing reflexes, and by persistence of intermittent fever, which started on the 6th day after birth and presented with peaks of over 42.5°C. Weight and length were always normal for age. There was a poor response to neurosensory stimuli. The general condition worsened during hyperpyrexia. On these occasions, contraction became more manifest, and particularly involved the face, jaw, and neck muscles, followed by an increase in dyspnea, with tachypnea, tachycardia, cyanosis, apnea, and occasional seizures and shock with generalized hypotonia. At the age of 2 months, the patient showed slight improvement. He could take small quantities of milk from a teaspoon and showed interest in some colored toys and followed them with his gaze, hinting at a smile. Though fevers persisted, episodes became less frequent.

Repeated EMG, performed on the left intercostal muscles and on several other muscles, demonstrated normal muscular activity. We tried to see whether the contraction would stop with the Vigevano maneuver,

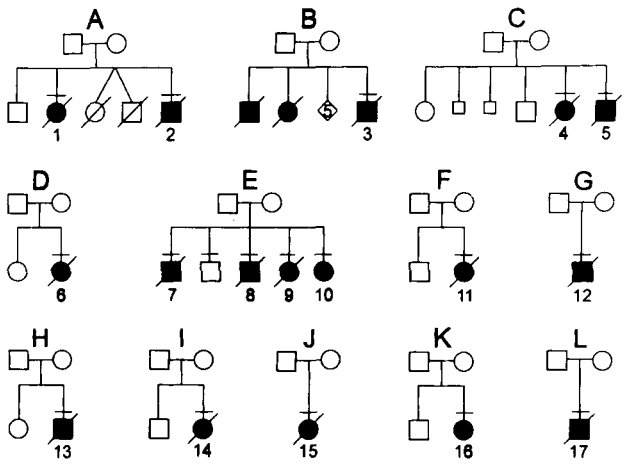

Fig. 1. **A–L:** Pedigrees of the 12 Sardinian families presented.

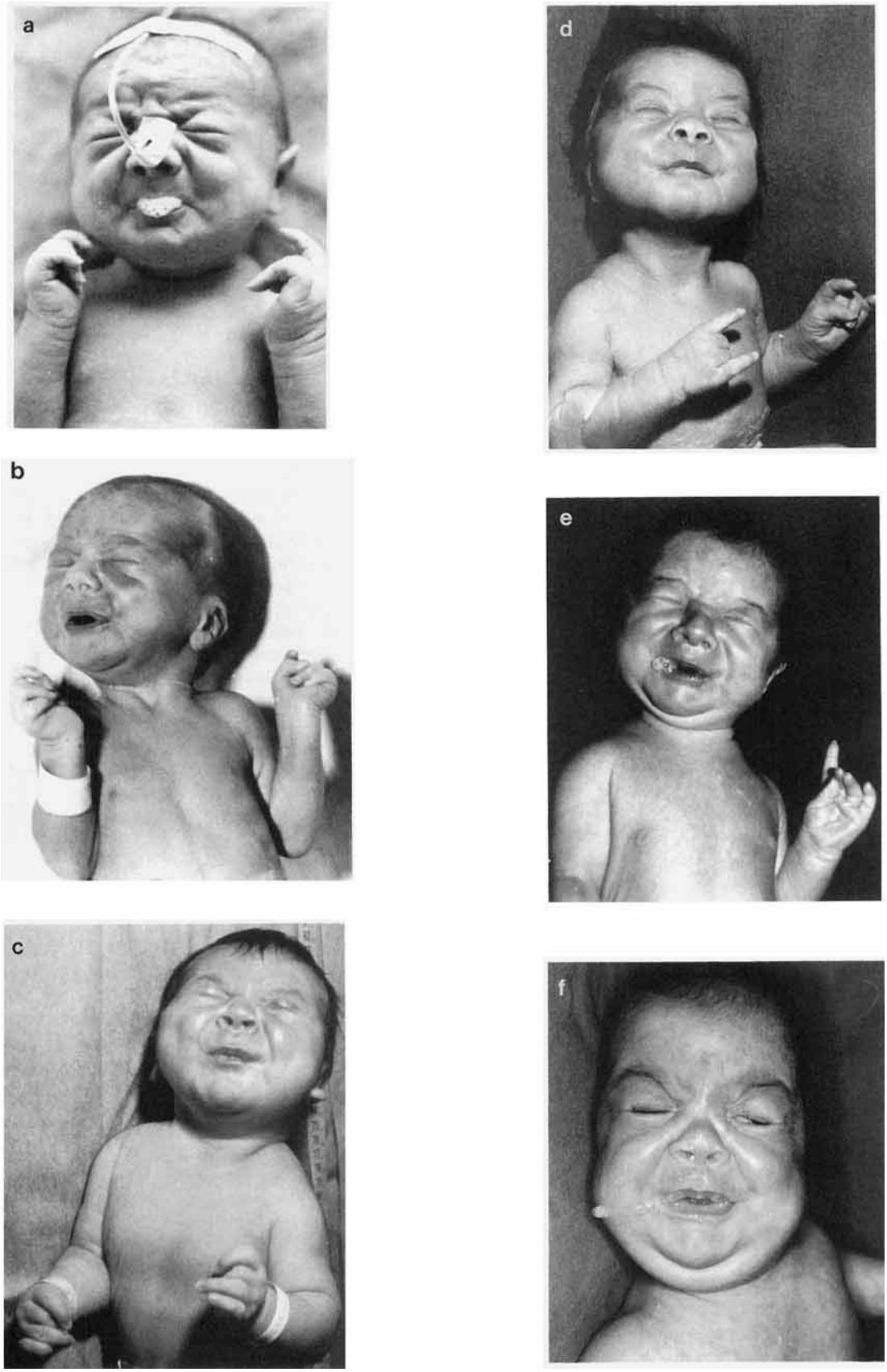

Fig. 2. **a,b,c,d,e,f:** Newborn Patients C-4, E-8, H-13, I-14, J-15, and K-16, respectively. Note the forced flexion of upper limbs, camptodactyly, and the identical facial expression during crying in the 6 patients.

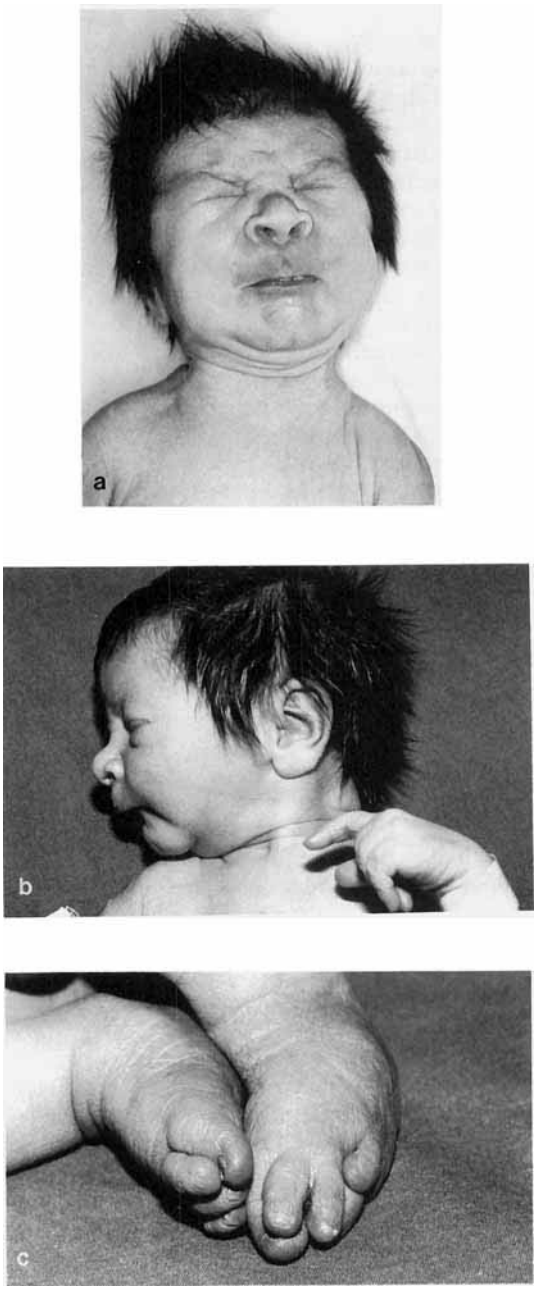

Fig. 3. **a:** Frontal view of patient L-17. Contractural spasms of facial muscles as in a tetanic crisis. **b:** Lateral view of the same patient. **c:** Feet of patient L-17 showing toe anomalies.

which immediately blocks contraction and seizures in the stiff-baby syndrome. This maneuver consists of a forced flexion of the head and lower limbs toward the trunk. In our patient, this action, rather than blocking the contractures, caused greater disturbance.

The concentration of GABA in the CSF was below the sensitivity of the method. Since low GABA levels have been described in startle disease, and in its neonatal form, the stiff-baby syndrome, and since there are documented therapeutic results with the use of vigabatrin, a drug that causes the GABA levels in the CSF to rise, we started this treatment. After doses of 400 mg/d for one month, we measured GABA levels in the CSF. Once more, it was undetectable and there was no clinical improvement. Dantrolene, a drug used in the treatment of malignant hyperpyrexia, was ineffective at a dose of 4 mg/d. Attempts at controlling muscle hypertonia with drugs such as diazepam, phenytoin, and phenobarbital were also ineffective.

Laboratory investigations including urine and blood amino acid chromatography, organic acids, and screening for lysosomal defects were normal. Homovanillic and 5-hydroxyindolacetic acids in the CSF were in the normal range. Biopsy of the vastus lateralis muscle, which was tested with different staining methods as well as with immunohistochemical reactions, was normal. Repeated brain ultrasound studies showed no anomalies. Brain MRI at one month revealed no anomalies.

DISCUSSION

The pattern of physical and neurological anomalies present at birth in all our patients clearly indicates a prenatal onset of the disorder. No alteration of fetal movements was reported. It was not possible to identify an environmental cause. There was no known prenatal exposure to infections, drugs, or other substances. Equal male and female incidence (8/9), pedigree analysis of the 12 families (Fig. 1), and absence of even minimal manifestations in the parents are consistent with a single gene causing this syndrome, probably inherited as an autosomal recessive condition. There is no consanguinity in the various families except in cases 6 and 17, both of whom came from a small village in Central Eastern Sardinia with a high percentage of inbreeding.

A differential diagnosis of all the common disorders that can manifest in the neonatal period with hypertonia and contractures was considered and excluded. These include neonatal tetanus, metabolic tetany, cerebral palsy due to severe perinatal asphyxia, and phenothiazine toxicity. Contraction at birth has also been described in the Schwartz-Jampel syndrome, Isaacs-Mertens syndrome, and in the stiff-baby syndrome. Moreover, muscle contractions are common in several congenital muscular dystrophies [Isaacs and Heffron, 1974].

The conditions most resembling our patients' findings are a group of congenital disorders with remarkable similarity. These are hyperekplexia or startle disease, the stiff-baby syndrome, and the Isaacs-Mertens or continuous muscle fiber activity syndrome. In addition, several authors have described a congenital disorder with autosomal dominant inheritance which resembles the stiff-man syndrome. The attacks of stiffness show continuous muscle activity, which can be abolished by diazepam [Bowler, 1959; Klein et al., 1972; Ryan et al., 1992]. Several authors consider the stiff-baby syndrome to be a neonatal form of hyperekplexia and have proposed the term hereditary stiff-baby syndrome. EMG in patients with this disorder shows continuous muscular activity, even in the absence of voluntary contractions, that can be eliminated by diazepam. This is in contrast to the continuous muscle fiber activity syndrome [Lingam et al., 1981; Andermann and Andermann, 1984; Tohier et al., 1991].

Hyperekplexia is characterized by an exaggerated startle response induced by auditory and tactile stimuli. Its onset is in early adulthood, but neonatal onset has also been reported. Newborn babies can manifest generalized muscular stiffness, myoclonic jerks, and apnea following contraction of the respiratory muscles [Sáenz-Lope et al., 1984; Gordon, 1993; Andermann and Andermann, 1984]. The neonatal-onset type can be fatal due to sudden and prolonged seizures leading to apnea resulting from contraction of the respiratory muscles. Vigevano et al. [1989] have proposed a maneuver consisting of forced flexion of the head and legs toward the trunk that instantly blocks the contractions and seizures. The mechanism of action of this maneuver is not known. It can be performed by the parents and often saves the patients from sudden death [Vigevano et al., 1989; Pascotto and Coppola, 1992; Cioni et al., 1993].

The stiff-baby syndrome is a hereditary disorder transmitted as an autosomal dominant trait with neonatal onset. The patient shows marked rigidity and fetal posture, due to flexion of the forearms and legs and fisting of the hands. A fixed look gives the child an expression of anxiety. Hypertonia is induced by tactile stimuli and is reduced during sleep and after general spinal anesthesia. Stiffening can affect the respiratory muscles and lead to apnea, sometimes causing sudden death. Regurgitation and vomiting can be associated with hiatal hernia. Inguinal, umbilical, and diaphragmatic hernias are often present due to increased intraabdominal pressure. Electroencephalogram (EEG) is normal, while EMG shows continuous muscle activity. Hypertonia generally disappears during the first years, but involuntary startle persists after sudden stimuli. There is a delay in walking. No lasting neurological or mental damage has been observed [Lingam et al., 1981; Cook and Kaplan, 1986; Tohier et al., 1991; Cioni et al., 1993].

The Isaacs-Mertens, or continuous muscle fiber activity syndrome, is inherited as an autosomal dominant trait and normally has onset at the age of about 30 years, but cases of neonatal onset manifested mainly by distal hypertonia accompanied by fasciculations have been described. EMG shows permanent activity of muscle not abolished by peripheral nerve block or anesthesia. Increased muscle tone and stiffness persist during sleep, as opposed to the stiff-baby syndrome. Treatment with carbamazepine and phenytoin remarkably reduces the symptoms [Isaacs and Heffron, 1974; McGuire et al., 1984].

In comparing these syndromes with our patients, some symptoms are noted to be very similar. For example, the contractions increase even after light stimuli and are already evident in the neonatal period. However, contractions observed in the stiff-baby syndrome involve almost all muscles, including respiratory and abdominal muscles. In the Isaacs-Mertens syndrome, hypertonia is usually distal, accompanied by fasciculation, and EMG shows continuous muscle fiber activity even in the absence of voluntary contraction. In our patients, the abdominal muscles are never involved and the stiffness of the limbs is less evident. In addition, contractions are never present in sleep or at rest, as opposed to the Isaacs-Mertens syndrome, and there are no EMG anomalies. In the stiff-baby syndrome and in hyperekplexia, stiffness is absent during sleep, but there are nocturnal jerks of the legs and persistence of fiber activity at rest. Treatment with diazepam, aimed at reducing continuous muscle activity, is effective in the stiff-baby syndrome but is not in the Isaac-Mertens syndrome, where carbamazepine and phenytoin are effective. All these drugs were ineffective in our patients. Hyperthermia, another typical symptom in our patients, has never been described in the above syndromes. We have considered the syndrome described by Froster-Iskenius et al. [1988], with hyperthermia associated with camptodactyly and sometimes with torticollis, but this seems to be a distinct entity, based on several differences.

The frequent elevations in body temperature up to 42°C indicated that malignant hyperthermia should be included in the differential diagnosis. This disorder occurs in susceptible patients following exposure to triggering drugs, such as inhalation anesthetics or depolarizing muscle relaxants. If the patient is not rapidly treated with dantrolene, a crisis characterized by muscle rigidity, rapid increase in body temperature, tachycardia, and raised CO_2 and blood potassium levels, followed by sudden death, occurs [Ball and Johnson, 1993]. Hyperthermia repeatedly occurred in all our patients in the absence of exposure to anesthetics. The use of dantrolene in patients 16 and 17 did not modify the fever fluctuations or the course of the disease.

The mode of inheritance also appears to differ. Both the Isaacs-Mertens and the stiff-baby syndromes are inherited as autosomal dominant traits, while for our patients we hypothesize autosomal recessive transmission. However, from the description of the patients described by Andermann et al. [1980], Sáenz-Lope et al. [1984], and Dalla Bernardina et al. [1988], some authors speculate that there are recessive forms of startle disease [Hayashi et al., 1991].

The pathophysiology of the condition we describe is not known, but as supposed for hyperekplexia, it is very likely to be linked to a lack of inhibition or to hyperactivity of brainstem centers, especially of the rhomboencephalic reticular formation [Gordon, 1993]. From the laboratory data of case 17, who showed a very low concentration of GABA in the CSF, we can speculate that the anomaly might be due to a congenital defect resulting in low concentrations of GABA [Dubowitz et al., 1992; Stephenson, 1992]. GABA is an important inhibitory neurotransmitter, and a decrease in its concentration could lead to hyperexcitability of the nervous system. In a linkage analysis of a large family with hereditary hyperekplexia, Ryan et al. [1992] and Shiang et al. [1993] located a gene responsible for the disease in the distal portion of the long arm of chromosome 5. This portion contains several genes for neurotransmitters, including genes for the 2 subunits of the GABA receptors, GABRA-1 and GABRG2. The gene involved in hyperekplexia codes for the α_1 subunit of the inhibitory glycine receptor (GLRA-1). In the central nervous system (CNS) of mammals, the inhibitory glycine receptor

is antagonized by strychnine, which causes hypertonia and symptoms similar to hyperekplexia when given in sublethal doses in the mouse. In individuals affected with hyperekplexia, 2 different mutations in exon 6 of the GRLA-1 gene have been found. These mutations involve substitution of an uncharged amino acid, leucine or glutamine, for arginine. In 50 nonaffected controls examined, no alteration was observed in exon 6. This arginine, at position 271 of the mature protein, is essential in chlorine ion uptake; its substitution with an uncharged amino acid reduces the transport of chlorine ions across the membranes. The beneficial results obtained by diazepam treatment can be explained by the fact that it acts as a GABA receptor inhibitor at the CNS level and compensates for the deficiency in glycinergic transmission [Ryan et al., 1992; Shiang et al., 1993]. We intend to investigate whether an analogous defect can be found in the presently described syndrome.

ACKNOWLEDGMENTS

The author thanks all colleagues who have helped him in treating these patients, and in particular, Dr. Francesco Muntoni for his precious help and advice.

REFERENCES

Andermann F, Andermann E (1984): Startle disease, or hyperekplexia. Ann Neurol 16:367–368.

Andermann F, Keene DL, Andermann E and Quesney LF (1980): Startle disease or hyperekplexia: Further delineation of the syndrome. Brain 103:985–997

Ball SP, Johnson KJ (1993): The genetics of malignant hyperthermia. J Med Genet 30:89–93.

Bowler D (1960): The "stiff-man syndrome" in a boy. Arch Dis Child 36:289–292.

Cioni G, Biagioni E, Bottai P, Castellaci AM, Paolicelli PB (1993): Hyperekplexia and stiff-baby syndrome: An identical neurological disorder? Ital J Neurol Sci 14:145–152.

Cook WP, Kaplan RF (1986): Neuromuscular blockade in a patient with stiff-baby syndrome. Anesthesiology 65:525–528.

Dalla Bernardina B, Fontana E, Colamaria V, La Selva L, Merlin D, Sgro V, Scarpa P (1988): Neonatal hyperekplexia. In Beaumanoir A, Gastaut H, Naquet R (eds): "Reflex Seizures and Reflex Epilepsies." Geneve: Editions Medicine & Hygiene, pp 409–414.

Dubowitz LMS, Bouza H, Hird MF, Jaeken J (1992): Low cerebrospinal fluid concentration of free gamma-aminobutyric acid in startle disease. Lancet 340:80–81.

Froster-Iskenius UG, Waterson JR, Hall JG (1988): A recessive form of congenital contractures and torticollis associated with malignant hyperthermia. J Med Genet 25:104–112.

Gordon N (1993): Startle disease or hyperekplexia. Dev Med Child Neurol 35:1015–1024.

Hayashi T, Tachibana H, Kajii T (1991): Hyperekplexia: Pedigree studies in two families. Am J Med Genet 40:138–143.

Isaacs H, Heffron JJA (1974): The syndrome of "continuous muscle fibre activity" cured: Further studies. J Neurol Neurosurg Psychiatry 37:123–125.

Klein R, Haddow JE, De Luca C (1972): Familial congenital disorder resembling stiff-man syndrome. Am J Dis Child 124:730–731.

Lingam S, Wilson J, Hart EW (1981): Hereditary stiff-baby syndrome. Am J Dis Child 135:909–911.

McGuire MSA, Tomasovic JJ, Ackerman N (1984): Hereditary continuous muscle fiber activity. Arch Neurol 41:395–396.

Pascotto A, Coppola G (1992): Neonatal hyperekplexia: A case report. Epilepsia 33:817–820.

Ryan SG, Sherman SL, Terry JC, Sparkes RS, Torres MC, Mackey RW (1992): Startle disease, or hyperekplexia: Response to clonazepam and assignment of the gene (STHE) to chromosome 5q by linkage analysis. Ann Neurol 31:663–668.

Sáenz-Lope E, Herranz-Tanarro FJ, Masdeu JC, Chacón Peña JR (1984): Hyperekplexia: A syndrome of pathological startle response. Ann Neurol 15:36–41.

Shiang R, Ryan SG, Zhu Y, Hahn AF, O'Connel P, Wasmuth JJ (1993): Mutations in the α_1 subunit of the inhibitory glycine receptor cause the dominant neurologic disorder, hyperekplexia. Nature Genet 5:351–358.

Stephenson JBP (1992): Vigabatrin for startle-disease with altered cerebrospinal-fluid free gamma-aminobutyric acid. Lancet 340: 430–431.

Tohier C, Roze JC, David A, Veccierini MF, Renaud P, Mouzard A (1991): Hyperekplexia or stiff-baby syndrome. Am J Dis Child 66:460–461.

Vigevano F, Di Capua M, Dalla Bernardina B (1989): Startle disease: An avoidable cause of sudden infant death. Lancet 1:216.